

THAT WHICH IS CLAIMED:

1. A method for determining the haplotype structure of a contiguous DNA segment comprising a first nucleotide polymorphism (NP) and a second NP separated by
5 at least 200 nucleotides, said method comprising:

- (a) obtaining a DNA sample comprising said contiguous DNA segment;
- (b) using said DNA sample as a template for polymerase chain reaction (PCR) amplification of a DNA fragment comprising said contiguous DNA segment;
- (c) ligating the ends of said DNA fragment to each other so as to produce
10 a circular DNA molecule; and
- (d) determining the haplotype of said first NP and said second NP.

2. The method of claim 1 wherein said first NP and said second NP are separated by at least 1000 nucleotides.
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3. The method of claim 2 wherein said first NP and said second NP are separated by at least 10,000 nucleotides.

4. The method of claim 3 wherein said first NP and said second NP are
20 separated by at least 30,000 nucleotides.

5. The method of claim 1 wherein said first NP and said second NP are selected from the group consisting of a substitution of five nucleotides or less, a deletion of five nucleotides or less, and an insertion of five nucleotides or less.
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6. The method of claim 5 wherein said first NP and said second NP each consist of a single nucleotide substitution.

7. The method of claim 1 wherein one or more additional NPs are located
30 between said first NP and said second NP.

8. The method of claim 7 comprising the additional step of determining the haplotype of said one or more additional NPs.

5 9. The method of claim 1 wherein said nucleic acid sample is from a human source.

10 10. The method of claim 1 wherein the fragment of step (b) is obtained by amplification of said segment from said DNA sample using long-range polymerase chain reaction (LR-PCR).

11. The method of claim 1 wherein the fragment of step (b) is cleaved using a restriction enzyme that does not cleave any nucleotide sequences occurring between said first NP and said second NP on said contiguous DNA segment.

15 12. The method of claim 1 wherein the haplotype of said first NP and said second NP on said circular DNA molecule is detected by restriction fragment analysis of said circularized segment or of a PCR amplification product using said circular DNA molecule as a template.

20 13. The method of claim 1 wherein the haplotype of said first NP and said second NP is detected by PCR amplification using primers whose ability to amplify segments from said circular DNA molecule is dependent upon the presence or absence of a particular haplotype at said first NP and said second NP.

25 14. The method of claim 1 wherein said first NP and said second NP are located in the same gene.

15. The method of claim 14 wherein the haplotype of each allele of said gene is determined.

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16. The method of claim 14, wherein at least one of said first NP and said second NP is associated with a clinically relevant phenotype.

17. The method of claim 14, wherein said gene is the TPMT gene.

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18. The method of claim 14, wherein said gene is selected from the group consisting of genes encoding beta2 receptor, apoE, OPRM1, and IL-4 receptor alpha.

19. A kit for determining whether a first NP and a second NP separated by at least 200 nucleotides are located on the same DNA molecule in a nucleic acid sample comprising:

(a) a first PCR primer capable of specifically annealing to a region of said DNA molecule adjacent to said first NP which is distal to said second NP;

(b) a second PCR primer capable of specifically annealing to the region of said DNA molecule adjacent to said second NP which is distal to said first NP;

(c) a polymerase enzyme capable of catalyzing the PCR amplification of a fragment of said DNA molecule between the annealing site of said first PCR primer and the annealing site said second PCR primer;

(d) ligase enzyme capable of catalyzing the ligation of a first end of said fragment to a second end of said fragment to form a circularized segment; and

(e) means for detecting the presence or absence of said first NP and said second NP on said circularized segment.

20. The kit of claim 19 further comprising a restriction enzyme, wherein said primers contain a restriction enzyme recognition site for said restriction enzyme.